REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended. Reconsideration is respectfully requested in light of the claim amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claim 1 has been rejected under 35 U.S.C. 112, first paragraph for failing to comply with the written description requirement. The Examiner suggests that the claim contains subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the amendment to define a dosage amount between 1 and 3 mg/kg appears to be new matter and further that unless there is evidence that the range is critical, the invention is further to be considered obvious. Applicants respectfully traverse this rejection.

The specification teaches at page 8, lines 14-33 the dose range of between 1 and 3 mg methotrexate per kg of body weight (mg/kg). In that section it is stated that the dosage "shown to be effective in these studies was low, 1 mg/kg." (see lines 14-15).

Then, the section goes on to state that the dose administered to rats, 1 mg/kg, was one quarter of the maximally tolerated dose in rats (lines 22-25). That means to one of skill that a dose as high as 4 mg/kg would be contemplated since the maximum tolerated dose is known by one of skill to be the dose that one does not want to exceed in order to administer a drug or agent safely to an animal. Then at page 9, Example 1, line 28, it is taught that the total dose administered to the animals and shown to be effective was two doses of 1 mg/kg, total dose of 2 mg/kg. Therefore, the specification as filed clearly defines doses to be used as between 1 and 3 mg/kg and therefore meets the requirements of 35 U.S.C. 112, first paragraph. However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 1 to recite that the dose used is 1 mg/kg per injection up to a total dose of 2 mg/kg per day. This amendment to the claim is clearly supported by teaching of the specification as filed as is not new matter as outlined *supra*. Moreover, as the specification points out, the dose claimed is a "low dose" and as such it would not be expected that this dose would have the therapeutic efficacy shown in the specification as filed. The prior art literature fails to teach use of methotrexate as claimed for treatment of lower back pain with radiculopathy at the low doses claimed. The claims as amended

meet the requirements of 35 U.S.C. 112, first paragraph and withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

The rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (1998) has been maintained for reasons of record. The Examiner suggests that Chamberlain et al. teach use of a dose of 2 mg and that since the claims are drawn to an animal, one that might weigh 2 kg would result in a dose of 2 mg using the dose range as claimed (1 mg/kg), a dose range that overlaps with the teaching of Chamberlain et al. Applicants respectfully traverse this rejection.

Chamberlain et al. teach administration of methotrexate to patients (humans) with leptomeningeal metastases presenting with radiculopathy, wherein the dose of methotrexate is administered intraventricularly and is a dose of 2 mg daily (total dose of 40 mg; approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual). The Examiner has also acknowledged in previous Office Actions that this reference fails to teach intrathecal administration of methotrexate and suggests that it would be unknown whether an injection subdurally

is into the back or the back of the head, and as such overlaps with the claimed invention.

In an earnest effort to advance the prosecution of this case, Applicants have amended the claim to recite that the dose of methotrexate is administered intrathecally into the spinal cord but not the brain. Support for this amendment can be found in the teachings of the general principles of human physiology and pharmacokinetics that intraventricular administration will not produce a local concentration of active drug in the spinal cord area that is anywhere near the same concentration as would be achieved with intrathecal administration. As discussed in the previous responses to Office Actions in this case, this is because, as taught in basic human anatomy and physiology texts (e.g., *Human Anatomy and Physiology*, Second Edition, Elaine N. Marieb (editor), Benjamin Cummings Publishing: Redwood City, CA, pages 404-405, starting at the second column on page 404) the circulation of cerebrospinal fluid through the brain ventricles is designed such that only a very small amount of the cerebrospinal fluid from the ventricles circulates into the central canal of the spinal cord. As is taught in this text, "most enters the subarachnoid space" (see page 404, second column, line 3-4 of second paragraph). Therefore, since intraventricular injection of methotrexate as

taught by Chamberlain et al. (1998) would result in only a small amount of circulation of the injected drug, via the cerebrospinal fluid, into the spinal cord, the concentration of methotrexate achieved would not be expected by one of skill in the art to be as high as could be achieved through direct administration into the spinal cord area via intrathecal administration. The subarachnoid space, as shown in Figure 12.20 on page 404 of the text cited above, is not the area touched through intrathecal administration. Most importantly, contrary to the Examiner's suggestion, one of skill would understand that intraventricular administration leading to subdural circulation is referring to the subdural area of the brain NOT the spinal cord. This is again a basic anatomical feature that allows for separation of the brain and spinal cord areas in the body. Therefore, Applicants, have amended the language of claim 1 to reflect the general principles of physiology and anatomy, and to be consistent with the teachings of the specification as filed where it is only taught to administer the methotrexate intrathecally.

Also in an earnest effort to advance the prosecution of this case, and as discussed *supra*, Applicants have amended the language of claim 1 to recite that the method involves administration of a dose level of 1 mg/kg per dose, not to exceed a total dose of 2

mg/kg each day. Support for these amendments to the claims is found at pages 8 and 9 of the specification as filed and was discussed in detail *supra*. Applicants, however, strongly disagree with the Examiner's suggestion that the reference of Chamberlain et al. teaches use of a dose range that overlaps with that of the instant invention.

Chamberlain et al. disclose only use of a 2 mg dose of methotrexate, intraventricularly. Nowhere in this reference is it suggested or taught that the 2 mg dose could be modified and given to any other species on the basis of mg drug per kg body weight. This is because, as taught only the specification as filed, one of skill would need to understand how efficacy related to safety in any particular species. That is why the teaching of the specification as filed is clear in defining dose on a mg/kg basis, to allow one of skill to understand how to extrapolate doses across different species. Chamberlain et al., however, is silent on this issue and thus would not be used by one of skill to extrapolate from a 2 mg dose in humans, which they would understand to be a dose of approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual. The 2 mg dose of Chamberlain et al. is much lower than the dose range claimed in the instant invention and as such would not be obvious to one of skill

in the art. It must be remembered that it is a general principle of pharmacology that you extrapolate doses across species based on mg/kg not mg alone. Therefore, one of skill would automatically convert the 2 mg dose of Chamberlain to its mg/kg dose and then dose another species based on that dose. Using this procedure, one of skill would administer a 2 kg animal a dose of 2 x 0.033 or 2 x 0.029 mg/kg which would be a dose of from 0.058 to 0.066 mg NOT 2 mg as suggested by the Examiner in the Office Action. Based on use of standard practice in the art of pharmacology, there is no overlap between any of the teaching of Chamberlain et al. and any dose range claimed in the instant invention.

In order to establish a *prima facie* case of case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly the reference cited fails to teach or suggest the invention as claimed. The reference cited, in fact, teaches a much lower dose range and a different route of administration. Therefore, this reference fails to teach the

limitations of the claim as amended and also fails to provide one of skill with an expectation of success. It is only with the specification in hand that one of skill would understand that intrathecal administration at that particular dose level would be effective for treating radiculopathy. Accordingly, this reference cannot make obvious the invention of the amended claim. Withdrawal of this rejection is respectfully requested.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, NJ 08053

856-810-1515